Synthesis and Complex Stability of Parent and *C*-Functionalised Derivatives of 1,4,7-Triazacyclononane-1,4,7-tris[methylene(methylphosphinic acid)]: an Effective New Complexing Agent

Christopher J. Broan, Karl J. Jankowski, Ritu Kataky and David Parker*

Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK

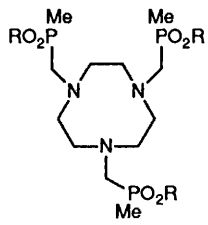
The title ligand forms kinetically stable complexes with indium and gallium and exhibits a marked selectivity ($10^{5.6}$) for binding Mg^{2+} over Ca^{2+} in aqueous solution.

There is considerable interest in the chemistry of aminoalkylphosphinic acids as analogues of the ubiquitous amino acids.[1] There are few reports of the complexation properties of these ligands[2] although the related phosphonic acid derivatives have been more thoroughly investigated.[3] With polyazamethylphosphonic acids [$R_2NHC_2PO(OH)_2$], complex stabilities are lower than those of the corresponding acetates although ligand basicities are higher. There is also a pronounced tendency for these ligands (with two basic groups per phosphorus) to form protonated metal complexes of moderate stability, therefore facilitating acid-mediated metal decomplexation. Notwithstanding the reported poor complexing ability for ethylenediamine-tetrakis(methylenephosphinic acid)[2a] and for the tetrakis[methylene(phenylphosphinic acid)] analogue,[2c]† the synthesis and complexation behaviour of the triazacyclononane and tetraazacyclododecane poly[methylene(methylphosphinic acids)] has been studied.[4] In addition *C*-functionalised analogues have been prepared bearing remote primary amine groups in order to permit subsequent derivatisation and protein linkage. This is with a view to preparing, for example, ^{111}In and ^{67}Ga radiolabelled antibodies for use in tumour imaging.[5,6]

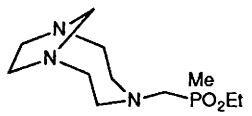
Reaction of 1,4,7-triazacyclononane with diethoxymethylphosphine and paraformaldehyde in dry tetrahydrofuran yields a mixture of **1a** and **2** which may be separated by chromatography on neutral alumina.‡ The triester **1a** exists as a mixture of two diastereoisomers (in a ratio of 5:2, as observed by ^{13}C NMR) which may be hydrolysed (6 mol dm^{-3} HCl; 18 h; 140 °C) to yield the triacid **1b** [δ_P (D_2O, pD = 0) 50.0; δ_C (D_2O) 19.43 (J_{CP} 93 Hz), 55.60, 59.06 (J_{CP} 92 Hz)]. Compound **1a** may also be prepared by alkylation of triazacyclononane with $BrCH_2P(Me)O_2Et$ [δ_P ($CDCl_3$) 47.1] or $MeSO_2OCH_2P(Me)O_2Et$ [δ_P (CD_2Cl_2) 42.9] (dimethylformamide; K_2CO_3; 60 °C; 6 h; 60%). The bicyclic tetrahydroimidazole **2** gave a diagnostic ^{13}C NMR resonance for the NCH_2N carbon at δ 76.2. The constitution of **2** [*m/z* (DCI) 262 (M^+ + 1); δ_H ($CDCl_3$ 4.20, 4.12 (d + d for the diastereotopic NCH_2N)] was confirmed by acid hydrolysis which yielded the monosubstituted amino acid **3** [*m/z* (FAB) 222 (M^+ + 1); δ_C (D_2O, pD 0.5) 19.65 (J_{CP} 85 Hz); 47.95, 49.56, 55.44 (CH_2N); 58.98 (J_{CP} 101 Hz)]. Its isolation may permit the synthesis of various other selectively functionalised triazacyclononane derivatives.

The reaction of (2*S*)-2-(4-benzamidobutyl)-1,4,7-triazacyclononane[6] with $MeP(OEt)_2$ and paraformaldehyde in tetrahydrofuran (THF) yielded **4a** as a mixture of two diastereoisomers [30%; *m/z* (DCI) 665 (M^+ + 1); δ_P ($CDCl_3$ 52.3, 51.4, 50.3, 49.9]. Hydrolysis (6 mol dm^{-3} HCl; 140 °C; 18 h) gave the amino acid **4b** and further reaction with bis-(*p*-nitrophenyl)succinate (Me_2SO, *N*-methylmorpholine; 20 °C; 3 h) yielded the active ester **4c**.

Admixture of equimolar quantities of **1b** and either $Ga(NO_3)_3$ or $In(NO_3)_3$ in aqueous solution (pH 2) yields the corresponding neutral complexes. The gallium complex [δ_P (D_2O, pD 1) 41.6; δ_C (D_2O) 19.6 (J_{CP} 101 Hz); 56.6, 60.1; 63.3 (J_{CP} 85 Hz)] may be observed by ^{71}Ga NMR spectroscopy in aqueous solution [δ_{Ga} + 136.3 ($w_{\frac{1}{2}}$ 215 Hz)] consistent with its high stability with respect to acid dissociation and the presence of a C_3 axis in the complex. Similar behaviour has been observed for the gallium complex of the tris(carboxymethyl) analogue.[7] The indium complex [δ_P (D_2O, pD 1) 39.1; δ_C 19.6 (J_{CP} 100 Hz); 58.0, 63.3 (J_{CP} 85 Hz)] was less stable with respect to acid-catalysed dissociation than [Ga·**1b**], but of comparable stability to the complex of the tris(carboxymethyl) analogue.[7]



1a; R = Et
b; R = H



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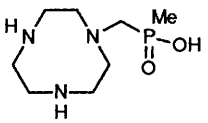

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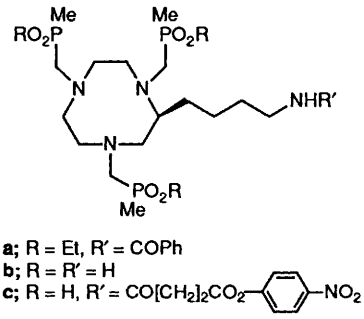

4a; R = Et, R′ = COPh
b; R = R′ = H
c; R = H, R′ = $CO[CH_2]_2CO_2$–C$_6$H$_4$–NO_2

Table 1 Protonation constants for ligand **1b** and binding constants for the complexes [298 K, H_2O, I = 0.1 mol dm^{-3} (Me_4NNO_3)

pK_1[a]	pK_2[b]	pK_3[b]	log K_{MgL}	log K_{MgLH}	log K_{CaL}
12.1	7.76	3.75	11.78	6.91	6.14

[a] Determined by ^{31}P NMR titration. [b] Determined by pH-metric titration followed by analysis using SCOGS-2 and SUPERQUAD.

† *Note added in proof:* preliminary ^{31}P NMR measurements suggest that the first pK_a for the phenylphosphinic derivative is ≥14.5 (and not 7.91 as reported[2c]), so that metal–ligand constants are considerably underestimated.

‡ All compounds gave satisfactory NMR (^1H, ^{13}C, ^{31}P) and mass spectral data in accord with the proposed structures.

Protonation and stability constants for complexation with Ca^{2+} and Mg^{2+} have been measured in aqueous solution (Table 1). The ligand is more basic than the related tris(carboxymethyl) analogue and exhibits a remarkable and pronounced selectivity to bind magnesium over calcium. The ratio of stability constants ($10^{5.6}$) is higher than was observed for the phosphonic acid analogue[3a] ($10^{4.6}$) and may be related to magnesium's preference for six-coordination and to the favourable binding interaction associated with the excellent donicity of the phosphorus-bound oxygen.

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